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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/167,516	10/06/1998	MARTIN A. CHEEVER	920010.448C8	1422

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EXAMINER	
CANELLA, KAREN A	
ART UNIT	**PAPER NUMBER**
1642	24

DATE MAILED: 05/08/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/167,516	Cheever et al
Examiner	**Art Unit**
Karen Canella	1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3 months* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☐ Responsive to communication(s) filed on _____.

2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under ***Ex parte Quayle***, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *7-12* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *7-12* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☒ Interview Summary (PTO-413) Paper No(s). *23*
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. After review and reconsideration, the finality of the Office action of Paper No. 20 is withdrawn.

2. The amendment filed October 10, 2002 has been entered. Claims 7, 8 and 9 have been amended. Claims 7-12 are pending and under consideration.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

4. Claims 10 and 12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "equivalent" in claim 10 is a relative term which renders the claim indefinite. The term "equivalent" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The ordinary meaning of the term "equivalent" would vary between practitioners in the art, therefore without an objective standard to ascertain the limitation of "equivalent" the metes and bounds of the claims cannot be determined.

5. Claim 10 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 10 is dependent on claims 7, 8 and 9. Claims 7, 8 and 9 are drawn to methods of enhancing an immune response comprising the administration of nucleic acids or cells expressing nucleic acids, wherein the nucleic acids are nucleotides 2026-3765 of SEQ ID NO:2 or DNA sequences which hybridize under moderately stringent conditions to said nucleotides. Claim 10 embodies the methods of claims 7, 8 and 9 wherein the polypeptide expressed for said nucleic acids has the amino acid sequence of SEQ ID NO:2 from residue 676

to residue 1255 or variants that produce at least an equivalent immune response. The specification states that "variants" have one or more deletions, insertions, substitutions or other modifications relative to the amino acid sequence of SEQ ID NO:2 from residue 676 to 1255 (page 12, lines 1-5). Thus, the scope of variant polypeptides is larger in scope than the polypeptides of any of claims 7, 8 or 9 which carry the limitation that the "entire amino acid sequence is from Her-2/neu and which is approximately the me length as Her-2/neu.

6. Claims 10 and 12 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

(A)As drawn to new matter

The amendment of August 4, 2000 added claim 12 which embodies the method of claim 10 wherein the polypeptide is a fusion protein with a peptide or polypeptide having immunogenic properties. The specification and claims as filed do not provide support for the claimed subject matter including a fusion protein having immunogenic properties. The specification contemplates only the expression of the her-2/neu polypeptide fused to thioredoxin reductase to increased stability of the recombinant protein in an E coli host cell. This is not adequate support for an amendment which contemplates a method of treatment comprising the administration of a nucleic acid or a cell expressing said nucleic acid, wherein the nucleic acid encodes a fusion protein and wherein the heterologous portion of said fusion protein is immunogenic. The thioredoxin reductase was not used as an immunogenic protein in a warm-blooded animal, but used to enhance the stability of the expressed protein in the environment of an E coli host cell.

(B)As drawn to written description.

Claims 10 and 12 are drawn to a method of eliciting or enhancing an immune response to a her-2/neu protein comprising the administration of a nucleic acid, vector comprising said nucleic

acid, or cell expressing said nucleic acid, to a warm-blooded animal, wherein the nucleic acid encodes a variant of the polypeptide comprising residues 676 to 1255 of SEQ ID NO:2. The method claims are therefore reliant upon a genus of nucleic acids encoding a variant polypeptide of residues 676 to 1255 of SEQ ID NO:2. The specification states that "variants" have one or more deletions, insertions, substitutions or other modifications relative to the amino acid sequence of SEQ ID NO:2 from residues 676 to 1255 (page 12, lines 1-5). The specification further states that in one embodiment, such variant are substantially homologous to the native her-2/neu protein and retain the ability to stimulate an immune response (page 12, lines 5-8). However, this recitation of an embodiment of a variant cannot be considered to limit the definition of variants to those that stimulate an immune response. Further, it is noted that the specification does not specifically state that the immune response which is stimulated is against the Her-2/neu protein. The specification does not limit the number of amino acid substitutions, deletions or insertions to the amino acid sequence of residue 676 to 1255 of SEQ ID NO:2, nor does the specification limit variants to those amino acid sequences evoking the same immune response as residues 676 through 1255 of SEQ ID NO:2. It is recognized in the art that an immune response can be divided into a innate, humoral or cellular response, or combinations thereof. Neither the specification nor claims limits the variants thereof of the polypeptide of claims 7, 8 and 9 to those evoking the same immune response as residues 676 to 1255 of SEQ ID NO:2. Thus, innate, humoral and cellular responses can be evoked by a molecule of the genus. The genus of proteins relied upon by the instant method claim is highly variant as it encompasses molecules having widely differing structures and evoking widely differing immune responses. The disclosure of residues 676 through 1255 of SEQ ID NO:2 does not anticipate the claimed genus because the genus is highly variant. One of skill int he art would conclude that applicant did not disclose a representative number of species falling within the genus to adequately describe such. Therefore, applicant was not in possession of the genu of proteins upon which the method claims rely.

7. Claims 7-12 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The instant claims are drawn to methods or elicitng or enhancing an immune response to Her-2/neu comprising the administration of a nucleic acid molecule or a viral vector to a warm blooded animal, administering a transfected antigen presenting cell to a warm blooded animal and administering an infected antigen presenting cell to a warm blooded animal.

The specification states on page 32, line 17 to page 33, line 7 that vectors for the delivery of the nucleic acids of the invention include recombinant viral vectors including retro viruses, adenovirus, pox virus, naked DNA, and nucleic acids associated with polycationic molecules and liposomes. The claims are clearly intended to encompass methods of gene therapy. However, the specification is not enabling for gene therapy as a method of elicitng or enhancing an immune response against her-2/neu.

The instant specification does not teach how to overcome problems with in vivo delivery and expression with respect to the administration of the claimed nucleic acids or viral vectors comprising said nucleic acids. The state of the art as of the priority date sought for the instant application is that in vivo gene delivery is not well developed and is highly unpredictable. For instance Verma et al (Nature, 1997, Vol. 389, pp. 239-242) teach that the Achilles heel of gene therapy is gene delivery. Verma et al state that the ongoing problem is the inability to deliver genes efficiently and to obtain sustained expression (page 239, column 3). Eck et al (Gene-Based Therapy, In: The Pharmacological Basis of Therapeutics, Goodman and Gilman, Ed.s, 1996, pp. 77-101) teach that the fate of the DNA vector itself with regard to the volume of distribution, rate of clearance into tissues etc., the in vivo consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA the level of mRNA produced, the stability of the mRNA produced in vivo, the amount and stability of the protein

produced and the proteins compartmentalization or secretory fate within the cell are primary considerations regarding effective therapy. Eck et al state that these factors differ dramatically on the vector used, the protein being produced, and the disease being treated (Eck et al bridging pages 81-82).

As of the priority date sought, it was well known in the art how to infect or transfect cells in vitro or ex vivo with viral vectors. However, using viral vectors to deliver DNA to an organism in vivo, or using infected or transfected cells to deliver nucleic acids which encode a particular protein sequence to an organism in vivo is in the realm of gene therapy, and as of the priority date sought, highly unpredictable in view of the complexity of in vivo systems. Orkin et al state ("Report and Recommendation of the Panel to Assess the NIH Investment in Research on Gene Therapy", NIH, 1995) that as of 1995, (two years after the priority date for the instant application) clinical efficacy had not been definitively demonstrated with any gene therapy protocol (page 1, second paragraph). Orkin et al defines gene therapy as the transfer of DNA into recipient cells either ex vivo or in vivo (page 7, under the heading "Gene transfer"), thus encompassing the instant claims drawn to the administration of antigen presenting cells transfected or infected ex vivo. Orkin et al concludes that in 1995, "none of the available vector systems is entirely satisfactory, and many f the perceived advantages of vector systems have not been experimentally validated. Until progress is made in thee areas, slow and erratic success in applying gene transfer methods to patients can be expected" Orkin et al comment that direct administration of DNA or DNA in liposomes is not well developed and hindered by the low efficiency of gene transfer (page 8, paragraph 5). Orkin et al teach that adequate expression of the transferred genes is essential for therapy, but that in 1995 current data regarding the level and consistency of expression of transferred genes in animal models was unknown. Orkin et al states that in protocols not involving ex vivo infections/transfection, it is necessary to target the expression of the transferred genes to the appropriate tissue or cell type by means of regulatory sequences in gene transfer vectors. The specification does not teach a vector having a specific

regulatory sequence which would direct the expression of the nucleic acids within the appropriate tissue type.

The specification does not remedy any of the deficiencies or the prior art with regard to gene therapy. Given the lack of any guidance from the specification on any of the above issues pointed out by Verma or Eck or Orkin. One of skill in the art would be subject to undue experimentation without reasonable expectation of success in order to practice the methods of claims.

8. All other rejections and objections as stated in Paper No. 17 are withdrawn.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (703) 308-8362. The examiner can normally be reached on Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Karen A. Canella, Ph.D.
Patent Examiner, Group 1642
May 5, 2003